IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Vendecruys et al.**	Confirmation No.: **7079**
Serial No.: **10/536,542**	Group Art Unit: 1618
Filing Date: **May 26, 2005**	Examiner: **Jake Minh Vu**

For: **Pharmaceutical Compositions Comprising a Basic Drug Compound, a Surfactant, and a Physiologically Tolerable Water Soluble Acid**

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 41.37

This brief is being filed in support of Appellant's appeal from the rejections of claims 21-42 dated December 17, 2009. A Notice of Appeal was filed on February 16, 2010.

1. REAL PARTY IN INTEREST

Janssen Pharmaceutica N.V.

2. RELATED APPEALS AND INTERFERENCES

None.

3. STATUS OF CLAIMS

This application was originally filed with claims 1-20. In the response filed January 5, 2009, claims 1-20 were canceled and claims 21-67 were added. Claims 43-67 were subsequently withdrawn and are pending. Claims 21-42 were examined. Claims 21-42 stand rejected. The rejections of claims 21-42, which stand together, are hereby appealed.

4. STATUS OF AMENDMENTS

No further amendments have been made subsequent to the amendments made in the Response filed September 16, 2009.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to pharmaceutical compositions that achieve improved oral bioavailability of basic drug compounds over those compositions of the prior art. Specification at page 3, lines 1-15. These compositions are semi-solids or solids (*id.* at page 108, lines 1-13) and comprise the basic drug compound (*id.* at page 4, lines 31-33), Vitamin E TPGS (*id.* at page 9, lines 5-6), and a physiologically tolerable water-soluble acid (*id.* at page 9, lines 14-19). The ratio of the acid:drug compound ranges from 1:1 to 100:1, by weight (*id.* at page 9, line 36-38).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The first issue on appeal is whether claims 21-29, 21, 32, and 34-42 are anticipated under 35 U.S.C. § 102(a) or § 102(e) by U.S. 6,919,370 (Chen 370). The second issue on appeal is whether claims 21-42 would have been obvious under 35 U.S.C. § 103 over WO 01/22938 (Verreck) in view of U.S. 6,828,301 (Chen 301) and WO 97/02017 (Clancy).

7. ARGUMENT

The Claimed Invention

The claimed invention is directed to semi-solid or solid pharmaceutical compositions that provide for surprising, improved oral bioavailability of a basic drug compound. Specification at page 3, lines 1-15. The compositions of the invention comprise, in addition to the basic drug compound, Vitamin E TPGS and a physiologically tolerable water-soluble acid. Claim 1. The acid:drug compound ratio ranges from 1:1 to 100:1 by weight. *Id.*

Claims 21-29, 21, 32, and 34-42 are not anticipated under 35 U.S.C. 102(a) or (e) by U.S. 6,919,370 (Chen 370)

Claims 21-29, 21, 32, and 34-42 are alleged to be anticipated under 35 U.S.C. § 102(a) or § 102(e) by U.S. 6,919,370 (Chen 370). The Appellants disagree and request withdrawal of the rejection and allowance of claims 21-29, 21, 32, and 34-42.

The law of anticipation is clear. A rejection for anticipation requires a showing that the invention is not new. *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009). "Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim. The requirement that the prior art elements themselves be 'arranged as in the claim' means that the claims cannot be 'treated as mere catalogs of separate parts, in disregard of the part-to-part relationships set forth in the claims and that give the claims their meaning. Unless a reference discloses . . . not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, (Fed. Cir. 2010).

The Examiner has not provided any evidence to support his conclusion that paclitaxel is a basic drug compound, as required by the claims. While the instant specification identifies paclitaxel as a drug that could be used in connection with the invention as broadly defined in the original claims, *i.e.*, where acidic and basic drugs were claimed, the pending claims are limited to embodiments that contain a basic drug compound, which would not include paclitaxel.

In the Office Action dated March 17, 2009, the Examiner appeared to be taking the position that Chen 370 is not limited to paclitaxel, citing to column 7, line 28 and line 43 of the reference. However, the section of the specification that the Examiner relies on does not identify compounds such as ciprofloxacin or AIDS drugs as compounds suitable for use in the formulation, but is instead identifying a list of drugs (other than paclitaxel) that may be solubilized by a "paclitaxel solubilizer." There is nothing in the Chen 370 reference to teach or suggest formulations that contain any active agent other than paclitaxel. Indeed, the title of Chen 370 is "Pharmaceutical Formulations Comprising Paclitaxel, Derivatives, and Pharmaceutically Acceptable Salts Thereof." Since the Chen 370 reference does not teach all elements of the claims, the rejection under Section 102 is improper.

Moreover, to the extent that Chen 370 is considered to teach all of the elements of the claims, it does not provide a sufficient disclosure of an embodiment in which all claim elements are as arranged as in the claim. The present invention is directed to solid or semi-solid compositions. Every Example described by Chen 370 is a liquid formulation, which the Examiner admits is clearly outside the scope of the claimed invention. ("Whereas the claimed invention requires the pharmaceutical composition to be a semi-solid or solid, Chen

Formulations 1-13 are directed to liquid concentrate formulations." December 17, 2009 Action at 3) Nevertheless, the Examiner cites to portions of the Chen 370 specification, outside the scope of the examples, that suggest solid, liquid, semisolid, gel, suspension, emulsion, or solution dosage forms would be acceptable for use with the invention described in Chen 370, overlooking the fact that no such formulations or methods for preparing them are provided in the reference. Clearly, the Examiner is treating the claims as a "catalog of separate parts," rather than identifying where, in a single reference, the invention is described as claimed. This improper application of the law of anticipation was error. The rejection is therefore improper and should be withdrawn.

Claims 21-42 are not obvious under 35 U.S.C. § 103 over WO 01/22938 (Verreck) in view of U.S. 6,828,301 (Chen 301) and WO 97/02017 (Clancy)

The Examiner Has Failed to Identify the Requisite Motivation to Combine the Cited References to Produce the Claimed Invention

Verreck describes basic drug compounds suitable for use as antivirals. Verreck indicates that these compounds can be melt extruded with one or more water-soluble polymers, for example hydroxypropyl methylcellulose (HPMC), to form particles. Verreck at page 1, lines 5-9; Example 4. These solid dispersions are said to be able to improve the bioavailability of the drug compound. Verreck at page 1, lines 11-13. Verreck suggests that addition salts can be made from the compounds described therein by combining the compound with an inorganic or organic acid. Verreck at page 10, lines 1-9. Verreck does not describe the use of Vitamin E TPGS.

Clancy is directed to controlled-release formulations of poorly soluble drugs. Clancy at page 2, lines 17-23. The formulations described in Clancy rely on a solid dispersion of the active compound in a hydrophilic poloxamer polymer. *Id.* These solid dispersions may be further combined with water swellable polymers such as hydroxypropylmethylcellulose (HPMC) (*id.* at page 7, lines 14-27) and a hydrophilic agent, for example, fumaric acid, citric acid, or tartaric acid, to further improve the release rate of the drug (*id.* at page 10, lines 10-15).

Importantly, neither Verreck nor Clancy describe the use of Vitamin E TPGS, a necessary requirement of the claimed invention that aids in the increased oral bioavailability, stability, and supersaturation profile observed with the claimed invention. Chen 301 teaches

that improved dispersion and dissolution performance can be achieved by adding a surfactant to a pharmaceutically composition that comprises a drug compound and an amine. Chen 301 at col. 15, lines 45-60, col. 15, line 61-col. 16, line 28. Vitamin E TPGS is identified in Chen as a compound that has surfactant properties. Chen 301 at col. 15, lines 45-60. Importantly, however, Chen 301 attributes the improved bioavailability described therein to the presence of the amine in the formulation, not to the surfactant: "It has been found that incorporation of a basic amine in a solid dosage form improves the in vitro dissolution rate significantly." Chen 301 at col. 41, lines 33-35.

The Examiner has failed to meet its burden in establishing a *prima facie* case of obviousness, *i.e.*, he has failed to demonstrate the requisite motivation to combine Verreck or Clancy with Chen 301 in order to arrive at the claimed invention. Verreck fails to describe the use of any surfactants. Indeed, Verreck relies on water-soluble polymers to form particles having improved bioavailability. Chen 301, while describing surfactants generally, identifies that improved oral bioavailability is achieved ***with basic amines***, not with Vitamin E TPGS and a physiologically tolerable water-soluble acid.

In cases where researchers "can only 'vary all parameters or try each of numerous possible choices until one possibly arrives at a successful result, where the prior art gives either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful,'" the Examiner "should not succumb to hindsight claims of obviousness." *P&G v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 996-97 (Fed. Cir. 2009). "Patents are not barred just because it was obvious to explore [a general approach] that seemed to be a promising field of experimentation where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* There is no suggestion or motivation in the cited art that would have led the skilled person to incorporate any surfactant, let alone the specific Vitamin E TPGS presently claimed, into the compositions described in Verreck. As the Examiner has failed to identify the any motivation to combine the cited references to arrive at the claimed invention, he has failed to establish the *prima facie* obviousness of the claimed subject matter. Accordingly, the rejection is improper and should be withdrawn.

The Unexpected Oral Bioavailability of the Compositions of the Invention Would Have Been Surprising and Unexpected to a Person of Ordinary Skill in the Art

Even if the Board finds that the cited references establish a *prima facie* case of obviousness over the cited art, and Appellants do not concede this point, obviousness may be rebutted based on "unexpected results" by demonstrating that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *P&G*, 566 F.3d at 994. Here, a showing of unexpected results sufficient to rebut a showing of obviousness has been presented to the Examiner during prosecution of the application.

As described in the Declaration of Marcus Brewster that was submitted on September 16, 2009, Vitamin E TPGS gave surprisingly higher average supersaturation as compared to Cremophor RH40 and Polysorbate 20 with this effect being seen over a range of compounds having varying physicochemical properties. Declaration of Marcus Brewster at ¶ 4. Vitamin E TPGS also provided better stability of the formed supersaturated solution than either Cremophor RH40 or Polysorbate 20. *Id.* at ¶ 5. Significantly, an oral bioavailability of ***100%*** was achieved with a composition of the invention, compared to only 30% and 60% achieved with PEG400 and Cremophor RH40, respectively, *Id.* at ¶ 7. This surprising result is also unexpected. *Id.* at ¶ 9.

Despite the Appellants showing of unexpected results, the Examiner summarily dismissed the data submitted for his consideration. The Examiner dismissed the Appellants' evidence, stating simply that it was "unpersuasive because Chen 301 teaches the prefer[red] surfactant is TPGS." Action at 4. Chen 301 notes that "Preferred surfactants include Vitamin E TPGS, Pluronic F68, or sodium lauryl sulfate, and mixtures thereof." col. 15, lines 56-58. Simply because a surfactant is identified as "preferred" does not provide any indication to the skilled person that the surfactant would demonstrate the unexpected supersaturation, stability, and oral bioavailability properties presently observed with Vitamin E TPGS, as used in the present invention. The Examiner summarily dismissed the presented evidence without setting forth sufficient facts and reasoning to justify his conclusion and improperly accorded the submitted evidence no weight, even though the evidence clearly "establish[ed] a nexus between the rebuttal evidence and the claimed invention." MPEP 2145. As the evidence of record clearly demonstrates the unexpected and surprising results achieved with the claimed invention, withdrawal of the rejection is requested.

Conclusion

Not only is the claimed invention non-obvious over the cited art, it surprising provides for higher average supersaturation, stability, and oral bioavailability of other compositions. The invention is patentable over the art and allowance of the examined claims is requested.

/Stephanie A. Barbosa/

Date: April 14, 2010

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8. CLAIMS APPENDIX

Claims 1-20 (Canceled)

21. (Previously Presented) A semi-solid or solid pharmaceutical composition comprising a basic drug compound, Vitamin E TPGS, and a physiologically tolerable water-soluble acid wherein the acid:drug compound ratio is ranges from 1:1 to 100:1 by weight.

22. (Previously Presented) The composition according to claim 21 wherein the basic drug compound, Vitamin E TPGS and the acid are intimately admixed.

23. (Previously Presented) The composition according to claim 21 wherein the physical state of said composition is a solid dispersion.

24. (Previously Presented) The composition according to claim 21 wherein the acid is citric, fumaric, tartaric, maleic, malic, succinic, oxalic, malonic, benzoic, mandelic, or ascorbic acid.

25. (Previously Presented) The composition according to claim 24 wherein the acid is citric acid.

26. (Previously Presented) The composition according to claim 21 further comprising an organic polymer.

27. (Previously Presented) The composition according to claim 26 wherein the polymer is selected from alkylcelluloses, hydroxyakylcelluloses, hydroxyalkyl alkylcelluloses, carboxyalkylcelluloses, alkali metal salts of carboxyalkylcelluloses, carboxyalkylcellulose esters, starches, pectins, chitosan, heparin, heparinoids, polysaccharides, polyacrylic acids and salts thereof, polymethacrylic acids and salts thereof, methacrylate copolymers, polyvinylalcohol, polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate, polyalkylene oxides, and copolymers of ethylene oxide and propylene oxide.

28. (Previously Presented) The composition according to claim 27 wherein the polymer is selected from methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, carboxymethylethylcellulose, sodium carboxymethylamylopectin, chitosan, alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gum arabic, guargum, xanthan gum, polyethylene oxide, polypropylene oxide, poloxamers, and poloxamines.

29. (Previously Presented) The composition according to claim 26 wherein the polymer has an apparent viscosity of 1 - 100 mPa.s when dissolved in a 2% aqueous solution at 20 °C.

30. (Previously Presented) The composition according to claim 26 wherein the polymer is hydroxypropylmethylcellulose.

31. (Previously Presented) The composition according to claim 26 wherein the polymer is a water soluble polymer having an apparent viscosity of more than 1,000 mPa.s when dissolved in a 2% aqueous solution at 20 °C and wherein the composition provides sustained release of the drug.

32. (Previously Presented) The composition according to claim 1 wherein the basic drug compound is no more than sparingly soluble in water.

33. (Previously Presented) The composition according to claim 1 wherein the drug compound is

4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]-benzonitrile;

4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile;

4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]-amino]-benzonitrile;

or a pharmaceutically acceptable salt or stereochemically isomeric form thereof.

34. (Previously Presented) The composition according to claim 1 wherein Vitamin E TPGS is present in a concentration of 1 to 70 % by weight relative to the total weight of Vitamin E TPGS, acid, and basic drug compound.

35. (Previously Presented) The composition according to claim 1 wherein Vitamin E TPGS is present in a concentration of 5 to 55 % by weight relative to the total weight of Vitamin E TPGS, acid, and basic drug compound.

36. (Previously Presented) The composition according to claim 1 wherein Vitamin E TPGS is present in a concentration of 10 to 50 % by weight relative to the total weight of Vitamin E TPGS, acid, and basic drug compound.

37. (Previously Presented) The composition according to claim 1 wherein the weight by weight ratio of Vitamin E TPGS to basic drug compound is in the range of from 100:1 to 1:5.

38. (Previously Presented) The composition according to claim 1 wherein the weight by weight ratio of Vitamin E TPGS to basic drug compound is in the range of from 50:1 to 1:2.

39. (Previously Presented) The composition according to claim 1 wherein the weight by weight ratio of Vitamin E TPGS to basic drug compound is in the range of from 10:1 to 1:1.

40. (Previously Presented) A pharmaceutical dosage form comprising a therapeutically effective amount of a pharmaceutical composition as defined in claim 1.

41. (Previously Presented) The dosage form of claim 40 wherein the dosage form is adapted for topical administration or administration into the nose, lungs, mouth, ear, stomach, rectum, or vagina.

42. (Previously Presented) The dosage form of claim 40 wherein said composition is filled into a standard capsule, or is mixed with at least one bulking agent and compressed into a tablet.

43. (Withdrawn) A method of treating a mammal with an oral pharmaceutical composition, comprising administering the pharmaceutical composition as a pharmaceutical composition according to claim 1 at any time of the day independent of any food taken in by said mammal.

44. (Withdrawn) A pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form as claimed in claim 1, and associated with said package, written matter non-limited as to whether the dosage form can be administered with or without food.

45. (Withdrawn) A process for preparing a composition according to claim 1 comprising:

dissolving a basic drug compound, Vitamin E TPGS, a physiologically tolerable water-soluble acid, and optionally a physiologically tolerable water-soluble organic polymer, in a solvent; removing the solvent from the resultant solution to form the resultant product; optionally forming the resultant product into desired shapes; and optionally coating the resulting product with a physiologically tolerable coating material.

46. (Withdrawn) The process according to claim 45 wherein the solvent is removed by spray-drying.

47. (Withdrawn) The process according to claim 45 wherein the solvent is removed by freeze-drying.

48. (Withdrawn) The process according to claim 45 wherein the solvent is a supercritical fluid.

49. (Withdrawn) A process according to claim 48 wherein the supercritical fluid is removed by decompression.

50. (Withdrawn) The process according to claim 48 wherein the supercritical fluid technology is Rapid Expansion of Supercritical Solutions or particles from Gas Saturated Solutions.

51. (Withdrawn) The process according to claim 45 further comprising adding a supercritical fluid, in addition to the solvent.

52. (Withdrawn) The process according to claim 51 wherein the supercritical fluid technology is Gas Anti Solvent, Solution Enhanced Dispersion by Supercritical fluids, Aerosol Solvent Extraction System, Supercritical Anti Solvent, or Precipitation with Compressed Antisolvent.

53. (Withdrawn) The process according to claim 45 wherein the solution is coated, sprayed or granulated onto a suitable carrier followed by evaporating the solvent.

54. (Withdrawn) The process according to claim 53 wherein the solution is granulated onto a suitable carrier followed by evaporating the solvent.

55. (Withdrawn) The process according to claim 53 wherein the solvent is evaporated by drying at elevated temperatures and/or under vacuum or by applying microwaves.

56. (Withdrawn) The process according to claim 53 wherein the carrier is microcristalline cellulose, fumed SiO_2, or an inert core.

57. (Withdrawn) The process according to claim 56 wherein the carrier is fumed SiO_2.

58. (Withdrawn) The process according to claim 53 wherein the process is carried out in a high shear granulator.

59. (Withdrawn) The process according to claim 45 wherein the process is performed in an extruder.

60. (Withdrawn) The process according to claim 59 wherein the solution of the components of the composition is granulated onto a suitable carrier and the resultant wetted powder is extruded.

61. (Withdrawn) A process of preparing a composition according to claim 1 comprising:

co-melting a basic drug compound, Vitamin E TPGS, a physiologically tolerable water-soluble acid and optionally a physiologically tolerable water-soluble organic polymer; and optionally forming the resultant product into desired shapes; and optionally coating the resulting product with a physiologically tolerable coating material.

62. (Withdrawn) The process according to claim 61 wherein the co-melting is performed by meltextrusion.

63. (Withdrawn) The process according to claim 61 wherein the resultant product is granulated, sprayed or coated onto a suitable carrier.

64. (Withdrawn) The process according to claim 61 wherein the resultant product is granulated onto a suitable carrier.

65. (Withdrawn) The process according to claim 64 wherein the carrier is microcristalline cellulose, fumed SiO_2, or an inert core.

66. (Withdrawn) The process according to claim 64 wherein the carrier is fumed SiO_2 .

67. (Withdrawn) The process according claim 61 wherein the process is carried out in a high shear granulator.

9. EVIDENCE APPENDIX

Declaration of Marcus Brewster.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Vandecruys, et al.	**Confirmation No.: 7079**
Application No.: 10/536,542	**Group Art Unit: 1618**
Filing Date: May 26, 2005	**Examiner: Jake Minh Vu**

For: Compositions Comprising a Basic Drug Compound, a Surfactant, and a Physiologically Tolerable Water Soluble Acid

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION PURSUANT TO 37 C.F.R. 1.132

I, Marcus E. Brewster, hereby declare as follows:

1. I am a Distinguished Research Fellow at Johnson & Johnson Pharmaceutical Research and Development (J&J PRD) based in Beerse, Belgium. I am currently the Head of ChemPharm Research and Early Development for Europe as well as the Chief Scientific Officer for the Chemical and Pharmaceutical division and have worked with Johnson & Johnson for 12 years. I am a Fellow of the American Association of Pharmaceutical Scientists, an former member and co-chairman of the Board of Scientific Advisors of the Controlled Release Society (2007-2009) as well as the current co-chairman of the Symposium/Workshop Committee, an Associate Editor of the Journal of Pharmaceutical Sciences (drug delivery and biopharmaceutics), a member of the Editorial Board of Die Pharmazie, a former theme editor for Advanced Drug Delivery Reviews, a member of various scientific societies and organizing boards (including the European Symposium for Controlled Drug Delivery and the International Symposium on Cyclodextrins) and the recipient of various recognitions including the J&J Excellence in Science Award (in 1998 and 2006), an Innovative Analytical Research Prize presented by FACCS (2003) and a PARC Prize for

Innovation in Pharmaceutical Analysis (2007). I have published over 245 peer-reviewed journal articles, book chapters and proceeding, have co-edited a monograph on solvents systems and their use for AAPS Press/Springer, presented over 350 meeting abstracts and was named as inventor or co-inventor on approximately 75 patents. I have also delivered more than 40 plenary lectures and 50 other invited presentations. I received my B.S. from Mercer University in 1978 and his Ph.D. from the University of Florida in 1982 in the field of Pharmaceutical Sciences. I was a visiting scientist at the Weizmann Institute of Science from 1996 to 1997.

2. I am an inventor of the above-referenced patent application. It is my understanding that the claims of the present application are directed to solid or semi-solid pharmaceutical compositions comprising a basic drug compound, vitamin E TPGS ("TPGS"), and a physiologically tolerable water-soluble acid. I also understand that methods of making these compositions are also claimed.

3. Under my direction and control, experiments were performed comparing the supersaturation effect of, for example, formulations of the present invention, on twenty-five developmental candidates having varying physicochemical properties, including molecular weight, TPSA, log P, pKa, and molecular volume. The results of these experiments were published in R. Vandecruys, et al., *Use of a screening method to determine excipients which optimize the extent and stability of supersaturated drug solutions and application of this system to solid formulation design*, Int'l J. Pharmaceutics 342 (2007) 168-175 ("Vandecruys").

4. TPGS tended to give a higher average supersaturation as compared to Cremophor RH40 and Polysorbate 20. Vandecruys at Table 2; page 172, col. 2. As this effect was seen over a range of compounds having varying physicochemical properties, I have concluded that this effect is general. That TPGS consistently gave higher average supersaturation results as compared to Cremophor RH40 and Polysorbate 20 is surprising and unexpected in view of what was known in the art.

5. TPGS also provided better stability of the formed supersaturated solution than either Polysorbate 20 or Cremophor RH40. Vandecruys at Table 3; page 173, col. 1. As this effect was seen over a range of compounds having varying physicochemical properties, I have concluded that this effect is general. That TPGS consistently provided better stability results as compared to Cremophor RH40 and Polysorbate 20 is surprising and unexpected in view of what was known in the art.

6. Solid formulations were also prepared to assess the oral bioavailability of Compound 1 using the dog as a model. Vandecruys at page 174, col. 1. Compound 1 is a poorly soluble weak base with a water solubility of 0.002 mg%. *Id.* at 173 at col. 1. Blends of drug compound with either PEG 400, Cremophor RH40, or TPGS were prepared. *Id.* at 174 col. 1. The oral bioavailability of the drug from each formulation was determined by comparing blood levels with those obtained using an IV dose of the compound. *Id.* at page 174, col 1.

7. The results of the dog bioavailability study are shown in Table 5 of Vandecruys. As set forth therein, solubilizing the compound in PEG 400 increased the oral bioavailability of the drug compound to about 30%. Solubilizing the compound in Cremophor RH40 resulted in an oral bioavailability of about 60%. Surprisingly and unexpectedly in view of what was known in the art, using TPGS, an oral bioavailability of about 100% was achieved.

8. Also under my direction and control, experiments were performed comparing the effect on supersaturation of, for example, TPGS, Tween 20 and Cremophor RH40, for itraconazole. The results of these experiments were published in M.E. Brewster et al. *Comparative interaction of 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin with itraconazole: Phase-solubility behaviour and stabilization of supersaturated drug solutions* Eur. J. Pharma. Sci. 34 (2008) 94-103 ("Brewster"). As shown in FIG. 10, formulations of itraconazole with TPGS exhibited very good levels and stability of supersaturation. See also Table 1 supporting robustness of the technique used.

9. Based on the foregoing, I concluded that solid or semi-solid compositions comprising a basic drug compound, TPGS, and a physiologically tolerable water-soluble acid exhibit extent and stability of supersaturation, and oral bioavailability profiles that are unexpected.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 15 September 09

Marcus E. Brewster

10. RELATED PROCEEDINGS APPENDIX

Not applicable.